NEW TRICYCLIC COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel pharmaceutical tricyclic compounds, pharmaceutical compositions containing them and methods for their use and methods for preparing these compounds. In particular, it relates to tricyclic 5-HT_3 receptor antagonists containing a bridged bicyclic amine substituent. The invention also relates to novel intermediates for making the new tricyclic compounds.

Background of The Invention

Compounds with highly selective actions on 5-HT (serotonin or 5-hydroxytryptamine) receptor subtypes show clear potential for therapeutic benefit and provide tools with which scientists can better understand the role of 5-HT in disease. A number of different 5-HT receptor subtypes have been identified. Some of these are designated as 5-HT_1, 5-HT_2 and 5-HT_3 receptors. Certain compounds having 5-HT_3 receptor mediating activity are useful for treating emesis, CNS disorders, cognitive performance disorders, drug dependency disorders, pain (e.g. migraine), cardiovascular disorders and gastrointestinal disorders. See, for example, an article entitled "Drugs Acting On 5-Hydroxytryptamine Receptors" appearing in The Lancet September 23, 1989.

Novel tricyclic compounds have now been discovered that are useful inter alia for treating a variety of conditions influenced by the 5-HT_3 receptor. The compounds of this invention are active at very low levels, particularly in the treatment of emesis but show also activity in the treatment of other disorders as shown below.

2. The compound of Claim 1 wherein
p is 0, 1 or 2;
n is 1 or 2;
q is 0;
R^1 is halogen, lower alkoxy or amino;
and if R^3 comprises
R^4 and R^5, they are each lower alkyl.

3. The compound of Claim 2 wherein n is 1.

4. The compound of Claim 3 wherein p is 0, the dashed line represents a double bond and if R^3 comprises R^4 and R^5 they are each methyl.

5. The compound of Claim 2 or 4 wherein R^3 is
1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or
endo-1-azabicyclo[3.3.1]non-4-yl.

6. The compound of Claim 5 wherein R^3 is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydro-cyclopent[*de*]isoquinolin-1-one.

7. The compound of Claim 6 which is 2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydro-cyclopenta[*de*]isoquinolin-1-one hydrochloride.

8. The compound of Claim 6 which is (*S*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydro-cyclopenta[*de*]isoquinolin-1-one hydrochloride.

9. The compound of Claim 5 wherein R^3 is 8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely, 2-(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-1,2,4,5-tetrahydro-cyclopent[*de*]isoquinolin-1-one.

10. The compound of Claim 9 wherein R^3 is *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely, 2-(*endo*-8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-1,2,4,5-tetrahydro-cyclopent[*de*]isoquinolin-1-one.

11. The compound of Claim 2 wherein n is 2.

12. The compound of Claim 11 wherein p is 0, the dashed line represents a double bond and if R^3 comprises R^4 and R^5, they are each methyl.

13. The compound of Claim 12 wherein R^3 is
1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicylo[3.2.1]oct-3-yl; or
endo-1-azabicyclo[3.3.1]non-4-yl.

14. The compound of Claim 13 wherein R^3 is 1-aza-bicyclo[2.2.2]oct-4-yl, namely 2-(1-azabicyclo[2.2.2]oct-4-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.

15. The compound of Claim 13 wherein R^3 is *exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely 2-(*exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.

16. The compound of Claim 13 wherein R^3 is endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely 2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.

17. The compound of Claim 13 wherein R^3 is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.

18. The compound of Claim 17 which is (*S*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one hydrochloride.

19. The compound of Claim 17 which is (*S*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one as the free base.

20. The compound of Claim 17 which is (*R*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.

21. The compound of Claim 13 wherein R^3 is *endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl, namely 2-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-2,4,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.

22. The compound of Claim 13 wherein R^3 is *endo*-1-azabicyclo[3.3.1]non-4-yl,namely 2-(*endo*-1-azabicyclo[3.3.1]non-4-yl)-2,3,5,6-tetrahydro-1*H*-benz[*de*]isoquinolin-1-one.

23. The compound of Claim 2 wherein p is 0, the dashed line represents two hydrogens, and if R^3 comprises R^4 and R^5, they are each methyl.

24. The compound of Claim 23 wherein R^3 is
1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or
endo-1-azabicyclo[3.3.1]non-4-yl.

25. The compound of Claim 24 wherein n is 1.

26. The compound of Claim 24 wherein n is 2.

27. The compound of Claim 26 wherein R^3 is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo-[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one.

28. The compound of Claim 1 wherein
n is 3;
p is 0, 1 or 2;
q is 0;
R^1 is halogen, lower alkoxy or amino;
and if R^3 comprises
R^4 and R^5, they are each lower alkyl.

29. The compound of Claim 28 wherein p is 0, the dashed line represents a double bond, and if R^3 comprises R^4 and R^5, they are each methyl.

30. The compound of Claim 29 wherein R^3 is
1-azabicyclo[2.2.2]oct-3-yl;
1-azabicyclo[2.2.2]oct-4-yl;
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; or
endo-1-azabicyclo[3.3.1]non-4-yl.

31. The compound of Claim 30 wherein R^3 is 1-azabicyclo[2.2.2]oct-3-yl, namely (*RS*)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5,6,7-hexahydrocyclohept[*de*]isoquinolin-1-one.

32. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 to 31 or 40 to 43, preferably in combination with a pharmaceutically acceptable excipient.

33. A method for treating a condition chosen from emesis, a gastro-intestinal disorder, CNS disorder, a cardiovascular disorder and pain in an animal in need of such treatment, which method comprises administering a therapeutically effective amount of a compound of Claim 1 to 31 or 40 to 43 or a composition of Claim 32 to such animal.

34. The method of Claim 33 wherein the condition is a gastrointestinal disorder.

35. The method of Claim 33 wherein the condition is a CNS disorder.

36. The method of Claim 33 wherein the condition is a cardiovascular disorder.

37. The method of Claim 33 wherein the condition is pain.

38. A method of treating emesis in a human undergoing cancer treatment using a cytotoxic pharmaceutical agent or radiation at levels sufficient to induce emesis, which method comprises administering an anti-emetic amount of compound of Claim 1 to 31, 40 to 43, or a composition of Claim 32 to such human.

39. A method for treating an animal having a condition in which the 5-HT_3 receptor plays a role, which method comprises administering a therapeutically effective amount of a compound of Claim 1 to 31 or 40 to 43 or a composition of Claim 32 to such animal.

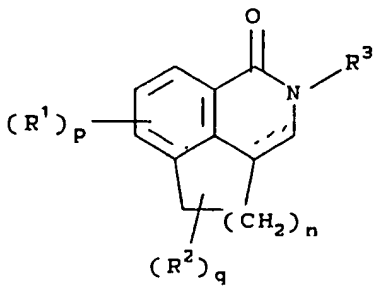
40. The *N*-oxide of the compound of Claim 1.

41. The compound of Claim 40 wherein
p is 0, 1 or 2;
q is 0;
R^1 is halogen, lower alkoxy or amino;
and if R^3 comprises
R^4 and R^5, they are each lower alkyl.

42. The compound of Claim 41 wherein p is 0, and if R^3 comprises R^4 and R^5, they are each methyl.

43. The compound of Claim 42 wherein n is 2 and R^3 is 1-azabicyclo[2.2.2]oct-3-yl.

44. A process for the preparation of a compound of Formula I



I

in which

n is 1, 2 or 3;

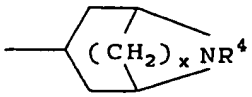
p is 0, 1, 2 or 3;

q is 0,1 or 2;

each R^1 is independently selected from halogen, hydroxy, lower alkoxy (optionally substituted with phenyl), lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;

each R^2 is lower alkyl; and

R^3 is selected from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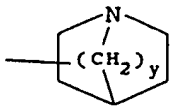
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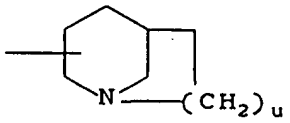
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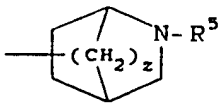

(d)

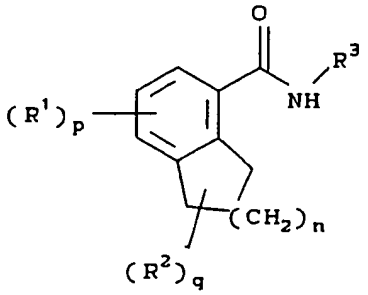
in which

u, x, y and z are all independently an integer from 1 to 3; and

R_4 and R_5 are independently C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, or a group $(CH_2)_tR_6$ where t is 1 or 2 and R_6 is thienyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C_{1-4} alkyl (optionally substituted by hydroxy, C_{1-4} alkoxy, carboxy, esterified carboxy or *in vivo* hydrolyzable acyloxy); or a pharmaceutically acceptable salt thereof or an *N*-oxide thereof, or an individual

isomer or mixture of isomers thereof, which process comprises one or more of the following steps:

(a) reactively contacting a compound of Formula II



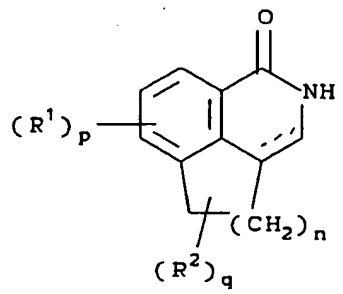
II

in which n, p, q, R^1, R^2, and R^3 are as defined above with a formylating agent in the presence of a strong base to form a compound of Formula I wherein the dashed line is a double bond,

(b) reducing the double bond represented by the dashed line in Formula I by hydrogenation to form a compound of Formula I wherein the dashed line represents 2 hydrogens,

(c) converting a salt of a compound of Formula I to the corresponding free compound,

(d) condensing a compound of the formula R^3L, wherein R^3 has the above meanings and L is a leaving group with a compound of the Formula XIII,



XIII

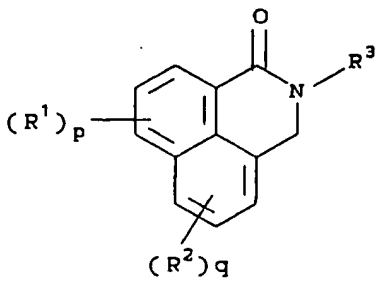
wherein R^1, R^2, n, p, q, and the dashed line have the above meanings,

(e) converting a compound of Formula I to the corresponding pharmaceutically acceptable salt,

(f) oxidizing a compound of Formula I to form the corresponding *N*-oxide of the R^3 component of Formula I, or reducing an *N*-oxide of the R^3 component to the corresponding amine,

(g) reducing a R^1 nitro substituent to a R^1 amino substituent or alkylating or acylating a R^1 amino substituent or alkylating a R^1 hydroxy substituent or dealkylating a R^1 alkoxy substitutent or debenzylating a R^1 benzyloxy substituent to the corresponding compound of Formula I,

(h) hydrogenating in positions 3a, 4, 5 and 6 a compound of the Formula XIV



XIV

wherein R^1, R^2, R^3, p and q have the above meanings,

(i) separating a mixture of isomers or diastereomers of a compound of Formula I into a single isomer or a diastereomer, or

(j) conducting any of steps (a) through (i) with optically active reactants.

45. A process according to Claim 44 wherein R^3 is selected from the group consisting of

1-azabicyclo[2.2.2]oct-3-yl;

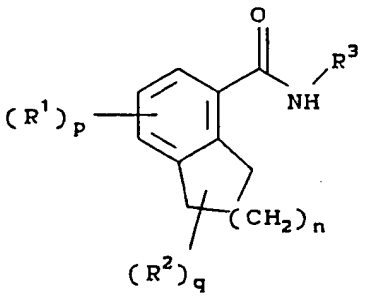
1-azabicyclo[2.2.2]oct-4-yl;

endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;

exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl; and

endo-1-azabicyclo[3.3.1]non-4-yl.

46. A compound represented by the formula



II

wherein

n is 1, 2 or 3;

p is 0, 1, 2 or 3;

q is 0, 1 or 2;

each R^1 is independently selected from halogen, hydroxy, lower alkoxy (optionally substituted with phenyl), lower alkyl, nitro, amino, amino